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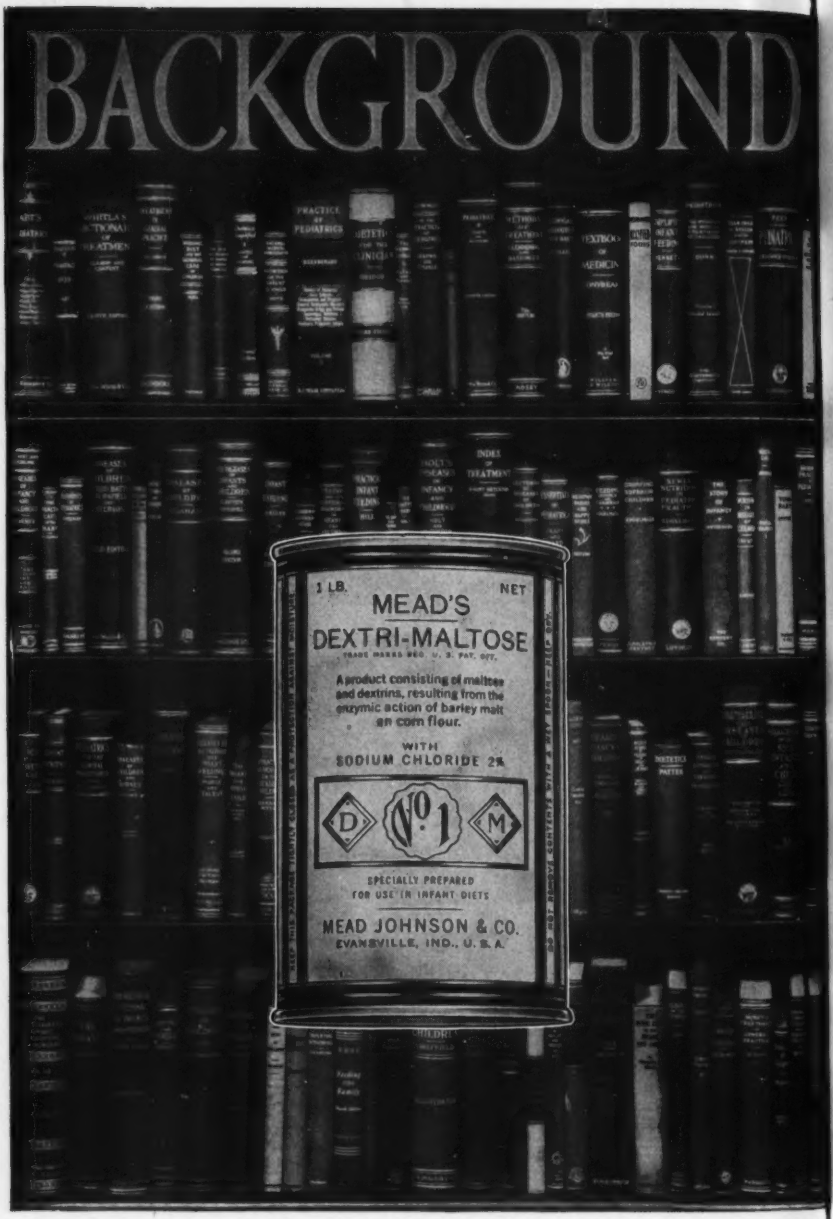

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ALLERGY AND IMMUNITY IN TUBERCULOSIS, WITH SPECIAL REFERENCE TO BCG VACCINATION*

SPECIAL REPORT

William A. Howard, M. D.

BCG, or the Bacillus of Calmette and Guerin, is an attenuated, viable strain of bovine tubercle bacillus which, when injected into guinea pigs or man, produces a typical host reaction that eventually results in the development of cutaneous sensitivity to tuberculin. In this respect it is the equivalent of a benign primary tuberculous infection acquired by natural means. Experimental investigators and clinical experiences have proved that a primary tuberculous infection confers a relatively significant resistance against a subsequent exogenous tuberculous infection, and it might be expected that an effective active immunization against tuberculosis would produce somewhat the same effect. The increasing employment of BCG vaccination in large numbers of individuals in the last two decades as an adjunct in the control of the disease has raised two very important questions concerning the basic relationships of allergy and immunity as observed in the tuberculous infections naturally occurring in man. The first question inquires into the nature of the immunity produced by the introduction of tubercle bacilli into the non-infected human host, and the relationship of this immunity to the hypersensitive state which develops as indicated by the presence of a positive tuberculin reaction. The second question considers whether or not the active production of tuberculin allergy and/or immunity in the previously non-infected individual is at all desirable. In order to arrive at a suitable appreciation of the importance of these two problems, a brief review of certain facts in the pathogenesis of tuberculosis is helpful.

Tuberculosis is essentially a biphasic disease, with primary and reinfection stages. The first effect of inhalation of virulent tubercle bacilli in the susceptible, non-infected host is the development of single or multiple foci of tuberculous pneumonia, usually adjacent to the pleura, with subsequent development of hilar lymphadenopathy. Together, the pulmonary and lymph node lesions constitute the primary phase or the so called "primary complex" as described by Ranke. Two to eight weeks after this first infection there develops a state of allergy or hypersensitivity to the tubercle bacillus, easily demonstrable by the occurrence of a positive cutaneous reaction to tuberculin in the previously tuberculin-negative individual. With the development of allergy, there is an alteration in the host response

* From the Allergy Clinic, Children's Hospital, Washington, D. C.

to the presence of tubercle bacilli, consisting of exudation, necrosis, and cavitation with a tendency toward healing by fibrosis. At some less well-defined time, but probably during the first year there also develops a partial immunity, not well defined or easily measured. It has been suggested that the primary infection so alters the reactivity of the organism that subsequent infection with large doses may kill, while smaller doses will produce either a marked location reaction or nothing at all. It is obvious, however, that there are many other variables which help to determine the susceptibility of man to reinfection.

Reinfection tuberculosis, or the reinfection phase, is the second stage in the development of the disease. Two definitions of the reinfection phase are possible, depending upon the importance ascribed to the development of the hypersensitivity described above. Customarily reinfection tuberculosis is taken to mean all subsequent infection with the tubercle bacillus once the initial primary focus has been brought under control. Hill and Stewart, however, prefer to include in the reinfection forms of tuberculosis all those lesions which make their appearance after the establishment of sensitization, and which extend beyond the limits occupied by the original primary lesions. In accordance with this definition, Hill classifies miliary tuberculosis, tuberculous meningitis, and tuberculous pneumonia as acute reinfection forms, and tuberculosis of bones and joints, renal tuberculosis, and chronic pulmonary tuberculosis as chronic reinfection forms. If the first three, miliary tuberculosis, meningitis, and tuberculous pneumonia are considered as constituting a progressive primary complex, then first infection with tuberculosis can be a truly dangerous disease. If Hill's classification is followed, then the primary complex is truly a benign infection. This differentiation is of considerably less significance, however, when it is appreciated that whether they are classed as progressive primary lesions, or acute reinfection forms, they still constitute the major cause of death from tuberculosis in children and young adults.

In the guinea pig, the primary infection produced by the introduction of virulent tubercle bacilli subcutaneously consists of a small nodule at the site of inoculation which subsequently ulcerates, with accompanying enlargement of regional lymph nodes. These nodes progress to caseation and necrosis, with further spread of tubercle bacilli, and death from massive generalized infection. If a second dose is given two weeks after the first, before the widespread infection has set in and after sufficient time has elapsed for the development of hypersensitivity, the local nodule produced by the second injection undergoes additional swelling, with necrosis and ulceration, and subsequent healing. The regional lymph nodes adjacent to the second inoculation are not enlarged, though tubercle bacilli will be found in them. This reaction to reinfection is known as the Koch phenom-

enon and can be produced in the sensitized guinea pig either by dead bacilli, tuberculin, or active infection. The relatively bland tuberculo-protein acts in the hypersensitive animal as a powerful irritant and necrotizing poison. The appearance of the Koch phenomenon in guinea pigs has given rise to the statement that the body once infected with tubercle bacilli resists reinfection, or stated another way, only living tubercle bacilli producing a mild infection can accomplish immunization. These statements imply that a primary infection with the development of hypersensitivity to tuberculin is accompanied by some degree of resistance or immunity to reinfection, and that such a state is desirable.

Raffell, in discussing the relationship of allergy to resistance in tuberculosis, states that measurable resistance to tuberculous infection can only be obtained by infection with attenuated living bacilli. Prolonged courses of injection of the many components of the tubercle bacillus, including the polysaccharides, unheated protein, phosphatide, wax, protein combined with phosphatide, bacilli from which lipids have been removed, defatted protein to which individual fats have been readded, and bacilli killed by moderate heat have failed to produce demonstrable resistance to infection. His conclusion is that the substance responsible for the acquisition of immunity is some heat labile factor in the organism, and that in its native form this is a complex and not a chemically distinctive compound. Other more recent experiments indicate that bacilli killed by heat, and by ultraviolet may have some immunizing properties.

Raffell has also demonstrated that hypersensitivity associated with tuberculous infection can be reproduced with dead whole bacilli, or with pure bacillary protein with wax added, but that in animals so treated, the hypersensitiveness was not accompanied by any detectable resistance. He thus comes to the conclusion that the two host responses are separate and independent phenomena.

Rich believes that allergy and immunity are separate and distinct and that hypersensitiveness may be destroyed without affecting the immunity. Both states develop as a result of infection, but they represent the response of the body to different elements in the tubercle bacillus, so that immunity is not achieved through allergy.

Willis and Woodruff, on the other hand, raise the question as to whether the hypersensitive, immune guinea pig who has been desensitized with large doses of tuberculin can withstand tuberculous infection as well as the allergic immune guinea pig. Earlier work seemed to indicate that the desensitized guinea pigs withstood infection equally well, but these authors believed that the experiments were not allowed to run long enough. In their own work, they found that during the first two months following reinfection, the allergic desensitized guinea pigs did about equally well, but

that after the third month, the desensitized guinea pigs began to die from extensive tuberculosis, with 100 per cent mortality in six months. The allergic controls lived considerably longer. It was noted that in the desensitized animals the lungs were almost totally destroyed, while the liver and spleen were usually devoid of tubercles, a picture just the reverse of tuberculous infection in the normal guinea pig. The suggestion was made that the lack of allergy was responsible for the free and unhibited growth of tubercle bacilli in the desensitized animals, indicating that allergy and immunity are at least related functions.

As pointed out by Long, the principal determinative factors in resistant and susceptible animals when infected with the tubercle bacillus appears to be the rapidity and intensity of the reaction produced at the site of inoculation (Koch phenomenon). The allergic response at the site of inoculation in the sensitized animal gives rise to the accelerated mobilization of phagocytic cells at the site of infection which may thus form an effective barrier to further spread of the infection. Thus, as Boyd states, some protective action may be ascribed to the allergic local reaction. It appears probable that in many if not all bacterial infections, hypersensitivity develops along with the development of immunity, but that the reaction is essentially a cellular one, independent of circulating antibody.

That the reaction of hypersensitivity to tuberculin is produced by a cellular antibody, and that it may be transferred by cells, but not by serum or cell-free exudates has been shown by Chase. The cells from an artificially stimulated peritoneal exudate and from spleen and lymph nodes, were taken from tuberculin sensitized guinea pigs, and after being carefully washed were injected into normal guinea pigs. By this method Chase obtained passive sensitization to tuberculin in sixteen of seventeen experiments. The intensity of the transferred sensitization varied with the number of sensitized cells injected and with the sensitivity of the donors. The serum of the donors failed to transmit the tuberculin reaction.

It is obvious that up to the present time, the final word on the relationship of allergy and immunity in tuberculosis has not been spoken. A clearer concept of the immunological features of the disease will probably come from further intensive studies employing the many components of the bacterial cell that is the tubercle bacillus. It would seem that immunity is more to be desired than freedom from infection, since the latter state always leaves an opening for subsequent infection to appear with disastrous results. Immunity is the master word in tuberculosis, and if it could be properly obtained, would be the logical successor to our present methods of control of tuberculosis.

It is now appropriate to consider the second problem concerning allergy and immunity in tuberculosis, namely, whether or not the active production

of tuberculin sensitivity in the previously tuberculin-negative individual is at all desirable. It is common practice to employ the allergic response to the tuberculin test as a measure of immunity, even though the relationship between the two is far from clear. It is evident that a primary infection with the tubercle bacillus, regardless of the method of introduction, is the initiating step in all future tuberculous disease. The body is able in most instances to resolve the first infection successfully but the allergy so produced is an essential antecedent for the development of reinfection tuberculosis. The assumption is that sufficient immunity is also established along with the hypersensitivity to enable the individual to overcome all ordinary future exogenous or endogenous infections unless they are massive, or unless some other factors alter body resistance.

One point of great importance in deciding the desirability of rendering individuals tuberculin positive is the fact that under modern conditions of infrequency of exposure the number of tuberculin-negative individuals is increasing rapidly. As a result, first infections with tubercle bacillus are being seen more often in young adults than in children. First infection in the second and third decades of life has many of the characteristics of chronic pulmonary tuberculosis, including localization, and a tendency toward cavity formation. Opinions vary as to its severity as compared to first infections as normally observed in childhood. In the United States at least, under the conditions that usually prevail, the prognosis for the first infection in the young adult is good, provided the lesion is discovered in the minimal stage. There appears to be a fairly general belief that morbidity and mortality rates from tuberculosis in young adults are greater in the tuberculin-negative group than in those who are tuberculin-positive. This may be due in part to a more rapid development of hypersensitivity upon the part of the host, with more prompt development of the acute reinfection forms of tuberculosis. One dissenting opinion is voiced by Myers and Stewart who found that in a group of children followed over a long period of time, tuberculous infection was nine times more common among tuberculin-positive children than among negative reactors. The significance of this statement is doubtful since it is only natural for tuberculin-positive children, remaining in their environment, to be subjected to more infection, while the tuberculin-negative group must remain in an environment essentially free of the disease.

A study of tuberculosis mortality rates indicates the well known fact that the lowest rate is to be expected during the age period of five to fifteen years. There is a low peak during infancy, and a gradually increasing mortality rate after the age of fifteen years. In the female this reaches its peak during the third decade of life, to be followed by a gradual decline up to age fifty, and another rise up to age 75 and over. In the male, the

mortality rate at thirty years is only slightly lower than in the female, but continues rising until a peak is reached at the age of sixty-five. More significant than the actual mortality figures, however, is the fact that the majority of tuberculosis deaths in infants and children are due to progressive primary infection (miliary tuberculosis, tuberculous meningitis, and tuberculous pneumonia). Terplan reported 35 deaths from tuberculosis in a series of 699 autopsies on infants and children, and found that 30 of the 35 deaths were due to primary infections. It is possible that a similar situation will obtain among young adults dying of tuberculosis, because of the ever-increasing number of first infections in this group.

While it is unquestionably better never to have become infected with the tubercle bacillus, it is certainly true that the individual who has successfully passed through a primary infection has put behind him the great danger that exists from the progressive primary or acute reinfection forms of the disease, whereas the individual who has not yet acquired a primary infection has these dangers yet to face. On the other hand, once the primary infection has been conquered, the individual is rendered allergic or hypersensitive, and is therefore liable to the increased hazards from chronic reinfection types of tuberculosis.

From the foregoing discussion, it is at once apparent that any method of vaccination against tuberculosis which could routinely and without danger produce a benign primary complex followed by the development of tuberculin allergy would at least eliminate the dangers of progressive primary or acute reinfection forms of the disease. There remains the question of which is the greater danger, the occurrence of a naturally acquired primary infection in the tuberculin-negative individual, or the hazard from reinfection forms which can appear only after the development of tuberculin sensitivity. While it is impossible to answer this question accurately, the impression is gained that naturally acquired primary infections are much the greater menace.

As previously stated, BCG, or the bacillus of Calmette and Guerin, is a strain of bovine tubercle bacillus which has been maintained in the avirulent state through many generations of subcultures. The method used at present in culturing the organism is that employed by the Pasteur Institute of Paris. The organisms are grown on bile-potato medium and transferred on plain potato medium and then on Sauton's medium, a synthetic medium composed of an amino acid (asparagine), glycerin, and buffered salts. After two transfers on synthetic medium, the organisms are gathered for the production of the vaccine. The organism was isolated in 1906, but its use in humans was not begun until 1921, since which time there has been a constant increase in the scope of its application. Comprehensive reports are now available from many countries, notably Sweden, Norway, Denmark, France and the United States, all of which have contributed to the

increased interest in and use of the vaccine in humans as a method of tuberculosis control. It is true that the ideal vaccine from the point of view of safety should be prepared from killed bacilli, though such a vaccine has not yet been proved effective in actual use. Encouraging results have recently been obtained with bacilli killed by moderate heat and by ultraviolet irradiation. Birkhaug and others have reported success with the use of a strain of tubercle bacillus isolated from the vole (any of the rodents of the genus Microtus, resembling and belonging to the same family as common rats and mice). The vole bacillus produces a relatively high protection against test infections with human tubercle bacilli, but the extent of the vaccination reaction indicates a somewhat lesser margin of safety than is known to exist with BCG vaccine.

BCG vaccine was originally given by the oral route, since it was felt that the intestinal mucosa would allow passage of the organism into the lymphatics. Regardless of the dose used, however, it was consistently noted that positive tuberculin reactions were obtained in only fifty to seventy-five per cent of the individuals so treated. As a result, the oral route of administration has largely given way to the intradermal or multiple puncture methods. The oral route, because of its great simplicity, is still useful in some instances, and for that reason is being retained as one of the standard methods of inoculation.

Much of the work thus far published on BCG deals with its introduction by the intracutaneous route, which consists of the injection of a measured amount of the vaccine into the skin in much the same manner as in a tuberculin test. The dose of vaccine administered has varied with the investigator, Wallgren using 0.05 mg. of the bacillary mass suspended in 0.1 cc. of normal saline, and Aronson and his co-workers using 0.10 to 0.15 mg. of bacillary mass per 0.1 cc. of normal saline. The results thus far reported using these varying doses have not differed significantly. The intracutaneous injection of BCG vaccine is followed in forty-eight hours by the appearance of a sharply defined reddened nodule measuring about 0.4 cm. in diameter and surrounded by a small area of redness. During the next two weeks the nodule increases slightly in size, while the area of redness decreases. After three to four weeks, the nodule rapidly increases in size and develops a central area of softening. In about seventy-five per cent of Aronson's cases, ulceration of this central area occurred. Healing required eight to twelve weeks, leaving a small soft scar which was apparently permanent. Regional lymph nodes were enlarged in a small percentage of cases, but none broke down. Subjective symptoms occasionally are present, and consist of pain at the site of inoculation, and fullness in the axilla. These symptoms disappear after healing of the local ulcer.

Because of the appearance of ulceration, and the subjective symptoms

reported, Rosenthal and his co-workers sought a different technique which might give equally good results, but with less difficulty for the recipient. These investigators decided upon the multiple puncture method, which was a modification of the scarification method often used in Europe. By this method a single drop of vaccine containing 15 mgms. of the bacillary mass per cubic centimeter is placed on the outer aspect of the upper arm, the skin of which has previously been cleaned with alcohol or acetone. The drop of vaccine is spread in linear fashion with the needle until it covers an area approximately 2 centimeters square. Punctures are then made in three rows of ten each, the rows being 4 to 6 millimeters apart. Bleeding should be avoided as in the technique for small pox vaccination. The vaccine is allowed to dry without blotting or covering, and the arm is kept dry for 24 hours. Grossly, no lesions are noted until 2 weeks after vaccination, at which time pin-point to pin-head sized macules appear, which become papular by the end of the fourth to sixth week. These regress rapidly leaving no scars or depressions. Regional lymph nodes are palpable two weeks after vaccination, but Rosenthal's reports state that they are never tender nor do they break down. Except for occasional local itching the recipient is usually unaware of the vaccination. The only report noted which gave less satisfactory reactions with the Rosenthal technique is the one which emanated from Uruguay, which described 12 cases of suppurating lymph nodes with local abscesses, which occurred up to eight months after the initial vaccination. Insufficient information is given to indicate whether there might not have been other reasons for such late lymph node suppuration.

Rosenthal has compared microscopically the development of the lesions produced by both the intradermal and multiple puncture techniques. In the former, because of the large number of organisms introduced at a single point, an area of edema and necrosis surrounded by a dense wall of polymorphonuclear leucocytes develops at the site of inoculation. These cells are seen to be so numerous as to partially block the lymphatic channels, retarding drainage and fostering further necrosis. The local abscess which forms may then break down and drain to the outside. By the multiple puncture technique the organisms are introduced more superficially, and, because of the multiplicity of foci, necrosis, blocking of lymph channels and abscess formation, are absent.

Regardless of which of the two methods of inoculation are used, a high percentage of positive reactors to old tuberculin or PPD is to be expected within two to four weeks. Some reports indicate as many as 99 per cent positive reactors. By either of these methods, therefore, one is able to produce a benign primary complex including the development of tuberculin allergy, just as occurs in the naturally acquired primary complex, but without any of the dangers of the latter.

The duration of tuberculin allergy following BCG vaccination is stated by Wallgren to be five to ten years, but it is apparently possible to vaccinate as often as every third year without fear of any untoward reaction, provided no naturally occurring tuberculosis has developed.

Without considering further the rationale of the use of BCG vaccination it is now appropriate to examine some of the studies which have been made and to review their results in terms of the efficacy of BCG in controlling tuberculosis morbidity and mortality.

The first requirement in the use of BCG vaccine is that the recipient be tuberculin-negative, usually to both the first and second strengths of Purified Protein Derivative, or to the 1–1000 and 1–100 dilutions of old tuberculin. With the acceptance of such individuals for vaccination, the studies so far reported have proceeded along one of two lines, with or without the use of controls. The bulk of the work done in children in the Scandinavian countries and in France, although they did apparently show a definite lowering of the tuberculosis morbidity and mortality rate, did not make use of strict controls, such as one might expect to be necessary in a procedure of such importance. Consequently, in the United States, all studies which have been performed have made full use of a control series in order to more fully evaluate the results. An additional refinement in the technique of the study has been practiced both in New York and Chicago, more notably in the latter city in the work of Rosenthal and his associates. They insisted that every individual to be vaccinated be not only tuberculin-negative, but should be in a tuberculin-free environment for several weeks prior to vaccination and remain in such an isolated situation after vaccination until the tuberculin test has become positive. This line of attack with suitable controls should give the most specific information about the effectiveness of the procedure. A more rigorous test of the effectiveness of the vaccine is its use in individuals who are negative reactors but who are left in their natural environments whether they are tuberculous or not. This type of experiment is perhaps more valuable from a public health standpoint, since BCG vaccine must be judged on the basis of whether it can adequately reduce tuberculosis morbidity and mortality under the most adverse circumstances. It is obviously impractical to apply any preventive vaccination generally if it is necessary to isolate all individuals who are receiving the vaccine for periods ranging from six to twelve weeks.

The first experiment in this country was begun in New York in 1926 by Park, Kereszturi and Mishulow, and later continued by Levine and his associates. Standards set up as fundamental in the study of the vaccine prophylaxis of tuberculosis were as follows:

1. The vaccine must be of standard potency.
2. There must be controls.

3. Controls and vaccinated cases should
   a. be selected by alternation to eliminate the possibility of bias,
   b. have identical follow-ups,
   c. come from the same locality,
   d. come from similar age groups,
   e. come from similar racial groups.
4. Contact with cases must be maintained.
5. Exposure conditions of patients must be known throughout the study period.
6. A reliable diagnosis of the cause of death must be obtained.

Levine reported that during the first ten years of the study, the selection of individuals for vaccination and for controls was entirely at the discretion of the physician assigned to the case, and it was felt that a tendency to vaccinate infants in the most cooperative families developed unintentionally. During this period of the study the tuberculosis mortality was almost five times as great in the controls as it was in the vaccinated group. During the last eleven years of the study, routine alternation of cases was the rule, the alternation being made before the cases were seen by the pediatrician. During this period the mortality rates were the same among the vaccinated and the controls. Levine and his co-workers felt that a statistical analysis of their figures indicated clearly that the cooperation of the vaccinated group in the earlier part of the study definitely influenced the results, and that with more or less equal cooperation in the latter part, this influence disappeared, with consequent equalization of the mortality figures. It was found to be impossible to employ routine isolation of the patients in the study although a few were managed in this manner. In the group in which such isolation was performed, results were comparable to the first part of the study in which a sharp lowering of tuberculosis mortality was noted.

A somewhat more comprehensive and more carefully controlled study has been carried out in Chicago by Rosenthal, and his associates. These investigators used newborn infants whose mothers had been followed in prenatal clinics for long enough periods of time to allow roentgenological examinations of every member of the household. The children in the first group studied came from families in which no tuberculosis was demonstrable by x-ray, and the infants were vaccinated or accepted as controls before they left the hospital. In this group the method of isolation until the tuberculin test became positive was not practiced. The second group of infants studied were those born into families where tuberculosis was demonstrated roentgenologically. Isolation of vaccinated and controls alike was practiced for six to twelve weeks until the tuberculous member of the family was sputum negative or was removed from the household.

During a ten year study of the patients in Group I, the vaccinated group produced a total of 11 cases of tuberculosis with one death, while among the controls there were 39 cases with 7 deaths. A comparison of the tuberculosis which did develop in both groups showed that in the vaccinated group no cases occurred under one and one-half years of age as compared to nine cases among the controls, three of whom died. The duration of the tuberculous process for all patients in the vaccinated group was less than one year, whereas in the control group eleven of twenty-five cases lasted from one to two years or longer. Calcification occurred earlier in the vaccinated group, and the individual lesions appeared to be smaller. From these observations it was concluded that in the vaccinated group not only is there a suppression of virulent tuberculous infection, but when infection does occur the lesions are less extensive and calcify earlier than the lesions in the control group.

In the second group of infants studied, those in which tuberculosis was present in the environment, all infants were isolated in foster homes for varying lengths of time depending upon the time required to improve the infants' own homes. In this smaller group of cases, there were two instances of tuberculosis with no deaths in the vaccinated group as compared with five cases and four deaths in the control group.

Considering the contact and non-contact groups as a whole, there were thirteen cases of tuberculosis and one death in the vaccinated group as compared with forty-four cases and eleven deaths in the control group. Phrased in morbidity and mortality rates, the morbidity rate per thousand person-years in the non-contact vaccinated group was 1.95 as compared to 6.46 for the controls. The mortality rates in the same groups were 0.17 for the vaccinated and 1.16 for the controls. In the contact group, the morbidity rate was four and one-half times as high in the controls, while mortality rates per thousand person-years was 17.6 in the controls as against zero in the vaccinated group.

From these results, Rosenthal and his co-workers believe it is a logical procedure to substitute the avirulent controlled dose of BCG vaccine for the virulent and uncontrolled natural infection. They especially advocate the vaccine for those racial groups which appear to be most susceptible, and those of all races and ages who are unduly exposed to the hazards of tuberculous infection. They also conclude that BCG vaccination is an entirely safe procedure.

One of the most significant studies on BCG is the one reported by Aronson, which was carried out entirely on North American Indians, a group known to have a naturally high morbidity and mortality rate from tuberculosis. All persons included in the experiment gave negative reactions to first and second strength purified protein derivative, but neither the vac-

cinated nor the control groups were isolated, either before or after the administration of the vaccine, and no changes were made in the mode of living except insofar as they occurred naturally over the period of nearly twelve years of the study. The only variable of significance in the study is the fact that the vaccine used was not standard, since batches were made at several different laboratories for use on different Indian reservations.

The vaccinated group consisted of 123 newborn infants and 1551 others ranging in age up to twenty years; 1457 Indians of comparable age and living under practically identical circumstances, together with 139 newborns constituted the control group; 0.1 to 0.15 mg. of BCG in 0.1 cc. of normal saline were given to the study group, and an equivalent amount of sterile normal saline was given to the controls. The intradermal technique was used, and although some ulceration and regional lymphadenopathy was noted, healing was complete by 12 weeks. Under the conditions of the experiment, neither the vaccinated group nor the controls were retested with PPD until one year following vaccination. At this time 93.3% of the vaccinated group gave positive reactions to either the first or second strength PPD, while in the control group, the percentage of positive reactors was 12.7%, these occurring as the result of natural infection. The high level of reactivity was maintained throughout the study in the vaccinated group, probably as a result of exposure to infection, while the increment of positive reactors in the control group was at the rate of about five per cent additional each year. It was felt that the sensitivity produced by BCG vaccine was not as marked as that produced by the naturally occurring infection.

Mortality rates from all causes were 3.1 per thousand person-years in the vaccinated group as against 7.2 in the controls. Of the fifty-five deaths in the vaccinated group, six were from tuberculosis, while in the control group there were 109 deaths, fifty-three of which were from tuberculosis. Mortality rates from tuberculosis were 0.4 per thousand person-years among the vaccinated and 3.5 among the controls. Among the 123 infants who were vaccinated there were seven deaths, none from tuberculosis, while in the 139 controls there were 15 deaths, four from tuberculosis.

While many criticisms might be directed at this study, especially from the point of view of adequate follow-up, lack of specific data on contacts with tuberculosis, and lack of adequate autopsy evidence of tuberculosis in some instances, it still appears that under the rigorous conditions of this experiment, and in a racial group of notorious susceptibility to infection, the results have been strikingly in favor of the efficacy of BCG vaccination.

A critical evaluation of these three studies, carried out under radically

different conditions, and employing different methods, indicates a preponderantly favorable response to BCG vaccine. With these encouraging reports at hand, interest in the prophylaxis of tuberculosis by vaccination has increased rapidly in the past few years, almost in the past few months, and it is hoped that such increased interest will lead to still further well controlled work on the subject.

A large number of reports on the use of BCG vaccine have been published by investigators in France, Norway, Sweden and Denmark, and to a lesser extent, in some of the South American countries. None of these studies represent anything like the ideal in which controls are present and all exposure conditions are known, but they indicate, even more clearly than the studies in the United States, the effectiveness of the vaccine in protecting patients who are constantly exposed to tuberculosis. Genevrier and Maclouf studied a group of student nurses in a Paris hospital and found that 46 of 77 nurses with negative tuberculins developed positive tuberculins during their service, thirteen of whom had clinical tuberculosis. A control group of 55 anergic nurses who received BCG vaccine showed no evidence of tuberculosis during their schooling. Courcoux and Duret reported a similar study over a three year period. Of sixty-four nurses who failed to react to tuberculin, thirty-three received BCG vaccine, while 31 remained as controls. During the period of the study, there occurred a single case of tuberculosis in the vaccinated group, in a nurse who failed to react to tuberculin after her first vaccination, and who developed only a slight allergy after re-vaccination. Among the controls there were 12 cases of clinical tuberculosis, an incidence of 38.7 per cent.

Troisier and Nico reported on a group of medical students in Paris, who could not be isolated either before or after the vaccine was administered. Of 322 students failing to give a positive tuberculin reaction, 174 were given BCG vaccine while 148 elected to act as controls. There were 13 cases of tuberculosis among the vaccinated students as compared with 27 in the controls, an incidence of 7.47 per cent as compared with 18.2 per cent.

A study recently completed in Oslo detailed the giving of BCG vaccine to 233 boys and girls aged 13 years, to be compared to a control group of 141 children of the same age. During a five year follow-up study, two cases of tuberculosis developed among the vaccinated children, while there were 77 cases among the controls. The conditions of the study were not stated in the abstract available, but from the number of cases developing, a high rate of contact must be assumed.

Malmros, writing of Swedish experiences, reported on a series of 22,413 persons vaccinated in a five year period. During this time, only one person admitted to the hospital with tuberculosis gave a previous history of

receiving the vaccine. Wallgren, whose experience exceeds that of almost all the continental writers, says that up to the present time nearly 750,000 persons in Sweden have been given the BCG vaccine, with definite lowering of tuberculosis morbidity and mortality, and that to date there is no evidence of the vaccine regaining its virulence. Wallgren also comments on the lack of controls in most of the Swedish studies by stating that failure to use BCG vaccine is considered poor medical practice, and that it is unfair to the patient to withhold the vaccine when its good effects are known.

Many additional reports are available, all of a similar nature. After reviewing these results of vaccination under many sets of conditions and in many different localities one can hardly escape the impression that regardless of the rather insecure foundation upon which the rationale of vaccination is built, the procedure has proved itself to be a valuable adjunct in the control of tuberculosis. One vagrant thought that has been voiced several times as an objection to the use of the vaccine, has been the fact that the development of a large percentage of positive reactors to tuberculin would destroy one of our principal weapons in case finding. The recent mass x-ray surveys have proven very practicable in replacing the tuberculin test, and further development of the technique of mass radiography with small films should make this procedure still more effective.

Wallgren sums up the case for BCG by stating that it gives protection against the immediate effects of a virulent primary infection (the progressive primary infection, or the acute reinfection forms of Hill), including primary pulmonary tuberculosis, miliary tuberculosis, and tuberculous meningitis, and to a certain extent against pleurisy and cavity formation insofar as they are sequels of a primary pulmonary infection. With regard to chronic reinfection forms, protection is afforded only against casual contact, and not much can be expected in prophylaxis against massive infections or in other conditions which may alter the susceptibility of the individual.

The resolutions passed by the First International BCG Congress at the Pasteur Institute in 1948, while a little enthusiastic, indicate the trend of thinking regarding the use of the vaccine. These resolutions were as follows:

1. Twenty-five years of continuous use has established the innocuity of BCG vaccine.

2. BCG vaccine constitutes the most effective means for preventing tuberculosis.

3. The Congress recommends the introduction of the vaccine through the skin, either by intradermal inoculation, scarification or multiple puncture.

4. The Congress does not exclude the oral route of administration because of its practicability.

5. It is desirable to re-vaccinate subjects whose cutaneous sensitivity to tuberculin has disappeared.

6. The Congress urges widespread diffusion of BCG vaccine.

7. The Congress recommends the development of all other measures employed in the fight against tuberculosis.

SUMMARY

The consensus of opinion among American authors appears to be that the vaccine deserves more extensive trial, but only by thoroughly qualified personnel and under rigid conditions. The vaccine is recommended where there has been a known exposure to tuberculosis or where exposure is likely to occur, in groups occupationally exposed such as medical students and nurses, and in selected population groups with high tuberculosis morbidity and mortality rates. The vaccination must always be confined to those individuals who fail to react to tuberculin. In all these studies it is necessary that adequate records be kept over long periods of time, and that both vaccinated and controls be followed over a long period of time. Only in such a manner may one eventually obtain the answer to the problem of the effect of BCG vaccine on the incidence of reinfection tuberculosis.

PARTIAL BIBLIOGRAPHY

1. Hill, Lee F.: Tuberculosis, in "The Child in Health and Disease." Grulee and Eley, Williams & Wilkins, Baltimore 1948.
2. Boyd's Text-book of Pathology, Lea and Febiger, Philadelphia 1947.
3. Ch'iu, P. T. Y., Myers, J. A., and Stewart, C. A.: The fate of Children with Primary Tuberculosis. J. A. M. A., **112**: 1306, 1939.
4. Willis and Woodruff: Tuberculosis in Allergic and Desensitized Guinea Pigs. Amer. Jour. Path., **14**: 337, 1938.
5. Chase, M. W.: The Cellular Transfer of Cutaneous Hypersensitivity to Tuberculin. Proc. Soc. Exper. Biol. & Med., **59**: 134, 1945.
6. Tuberculin Allergy, Editorial. J. A. M. A., **138**: 823, 1948.
7. Raffell, S.: A Study of the Relationship of Resistance, Allergy, Antibody and Tissue Reactivity in Tuberculosis to the Components of the Tubercle Bacillus. Calif. Med., **65**: 13, 1946.
8. Long, Esmond R.: Recent Advances in the Fundamental Knowledge of Tuberculosis. Paper delivered before the International Congress on Tropical Medicine and Malaria, Washington, D. C., May 10, 1948.
9. Birkhaug, K.: Vaccination with the Vole Bacillus. Am. Rev. of Tuberc., **54**: 41, 1946.
10. BCG Vaccination, Editorial. J. A. M. A., **138**: 512, 1948.
11. Rosenthal, S. R., Blahd, Margery, and Leslie, Eleanor I.: Ten Years' Experience with BCG (Experimental and Clinical). J. Pediat., **26**: 470, 1945.

12. Rosenthal, S. R.: Vaccination against Tuberculosis by BCG (Bacillus of Calmette and Guerin). Amer. Pract., **2:** 462, 1948.
13. Wallgren, Arvid: BCG Inoculation and BCG Vaccination. Am. Jour. Dis. Child., **76:** 485, 1948.
14. Wallgren, Arvid: Twenty Years of Vaccination with BCG in Sweden. Annales Paediatrici, Basel, **170:** 57, 1948.
15. Wallgren, Arvid: Vaccination with BCG in Sweden. Paediat. Danub., **1:** 193, 1947.
16. Wallgren, Arvid: BCG Vaccination, Is It of Any Value in the Control of Tuberculosis. Brit. M. J., **1:** 1126, 1948.
17. Wallgren, Arvid: Vaccination with BCG in Sweden during the Second World War. La Semaine des Hôpitaux, **22:** 369, 1946.
18. Rosenthal, S. R., Leslie, Eleanor, I., and Loewinsohn, E.: BCG Vaccination in All Age Groups. Methods and Results of a Strictly Controlled Study. J. A. M. A., **136:** 73, 1948.
19. Levine, Milton I.: The Present Status of BCG in the Prophylaxis of Tuberculosis. N. Y. State Med. Jour., **47:** 1771, 1947.
20. Levine, and Sackett: Results of BCG Immunization in New York City. Am. Rev. Of Tuberc., **53:** 517, 1946.
21. Aronson, J. D.: Protective Vaccination against Tuberculosis with Special Reference to BCG Vaccination. A. Rev. Tuberc., **58:** 255, 1948.
22 Aronson, J D.: Present Status of BCG Vaccine in the Prevention of Tuberculosis. Penns. Med. Jour., **51:** 502, 1948.
23. Wilson, G. S.: The Value of BCG Vaccination in Control of Tuberculosis. Brit. M. J., **2:** 855, 1947.
24. Ferguson, R. G.: BCG Vaccinations in Hospitals and Sanatoria of Saskatchewan., Canad. J. Pub. Health, **37:** 435, 1946.
25. McKone, B.: BCG in the Prevention of Tuberculosis. Canad. Med. Assn. Jour., **58:** 537, 1948.
26. Malmros, H., Efficacy of BCG Vaccination. Brit. M. J., **1:** 1129, 1948.
26. de Assis, Arlindo: Oral Vaccination of Newborn Infants. Correspondence, J. A. M. A., **138:** 89, 1948.
27. Troisier, J., and Nico, J.: Antituberculous Immunization of Medical Students with BCG. Le Semaine des hôpitaux, **22:** 372, 1946.
28. Courcoux, A., and Duret, M.: The Immunization of Nurses with BCG. La Semaine des hôpitaux, **22:** 366, 1946.
29. Courcoux, A.: Extension of prophylaxis of Tuberculosis by the BCG Bacillus to Adolescents and Adults. Presse Medicale, **56:** 410, 1948.
30. Walsz-Hockert, O.: Duration of Immunity after Vaccination with BCG. Acta Paediatrica, **35:** 89, 1948.
31. Blanch, Blanch, and Seremini: Suppurating Lymph Nodes. Complications of BCG Vaccination, Rosenthal Technique. Revista de Tuberculosis del Uruguay, **16:** 85, 1948.
32. Birkhaug, K.: BCG and the Newer Epidemiology of Tuberculosis. Bull. New York Acad. Med., **24:** 411, 1948.
33. Neiman, I. S., and Loewinsohn, E.: Inhibition of Primary Tuberculosis by BCG. A Study in Children based on 13,470 Chest Roentgenograms Am Rev. Tuberc., **46:** 27, 1947.
34. Hertzberg, G.: Recent Experiences with BCG Vaccine in Norway. Tubercle, **28:** 1, 1947.

35. First International BCG Congress, Pasteur Institute, J. A. M. A. **138**: 228, 1948.
36. Irons, E. E.: BCG Vaccination Among Medical and Nursing Students. Am. Jour. Dis. Child., **77**: 376, 1949.
37. Rosenthal, S. R.: Methods of BCG Vaccination and Production. Am. Jour. Dis. Child., **77**: 377, 1949.
38. Black, Robert A.: BCG Vaccination in Chicago. Am. Jour. Dis. Child., **77**: 381, 1949.
39. Tuberculosis Vaccine. Life Magazine, May 2, 1949.
40. Huet, G. J.: Childhood Infection and Adult Tuberculosis. Maandschr. v. Kindergeneesk., **15**: 339, 1947.

WILMS' TUMOR IN A FIVE WEEKS OLD INFANT

Case Report No. 155

Hassan Ahari, M.D. C. G. 49–184
Morris I. Michael, M.D.

Embryonal adenomyosarcoma or Wilms' tumor is the typical renal tumor of childhood which, because of its insidious onset, rapid growth and often late recognition, carries with it a very grave prognosis. Earlier recognition and treatment offer the best hope of decreasing the mortality in this very malignant process.

In a series of 17 cases described by Kretschmer [1] the youngest patient was 3 months old. Ewing [2] notes that Schaffer described the early stage of the disease in a single kidney of a deformed fetus. In 24 cases seen at Children's Hospital between 1934 and 1948 the youngest was 5 months old.[3]

It is of interest therefore to present the following case of Wilms' tumor removed from a five weeks old premature infant.

C. G., a five weeks old white male, was admitted to Children's Hospital on January 4, 1949 because of vomiting and an abdominal mass.

The history revealed that the infant was apparently well until three weeks of age when he began to vomit once or twice daily. The vomiting was projectile in nature and would usually occur immediately after feeding while the mother was attempting to "burp" him. At times he would vomit a small quantity about an hour after feeding. The infant was examined by one of us five days prior to admission and a small mass, the size of a plum, was observed in the right upper quadrant. At that time a pyloric tumor was considered and an atropine preparation prescribed with prompt improvement the next day. Five days later the child was seen again because of recurrent vomiting. On examination the mass was found to have grown in size to that of an orange. Bowel movements have been normal; however, the infant had been given rectal suppositories for constipation on a few occasions

Past history revealed that the patient was the product of seven months gestation; labor started after the obstetrician attempted to rotate the baby externally because he was in the transverse position. Birth weight was 2400 grams. He was placed in an oxygen tent for the first two days. He remained in the hospital for two weeks and gained 180 grams during this period on an Alacta formula.

Family history revealed an allergic manifestation (hives) in the mother. There was one sibling from a previous marriage of the father.

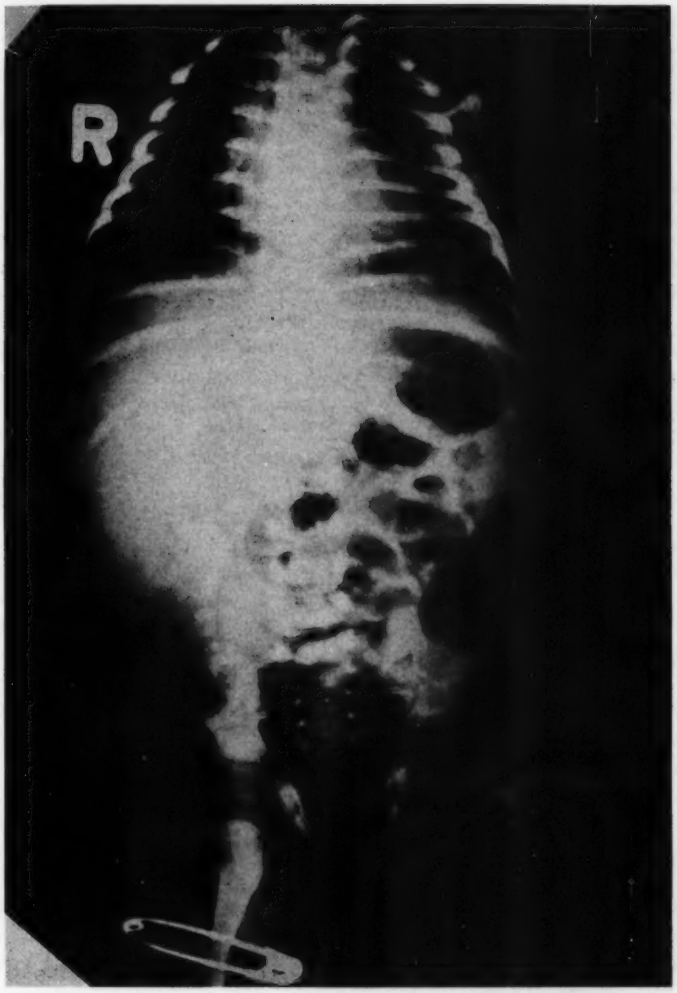

FIG. 1: C. G. Flat plate of the abdomen shows the radiodensity of the tumor mass occupying the right side of the abdomen with marked shift of the intestinal tract to the left.

Physical examination disclosed a well developed, well nourished white baby of stated age weighing 3,030 grams. The temperature was 99.8 degrees F. A distended abdomen was evident. Palpation revealed a

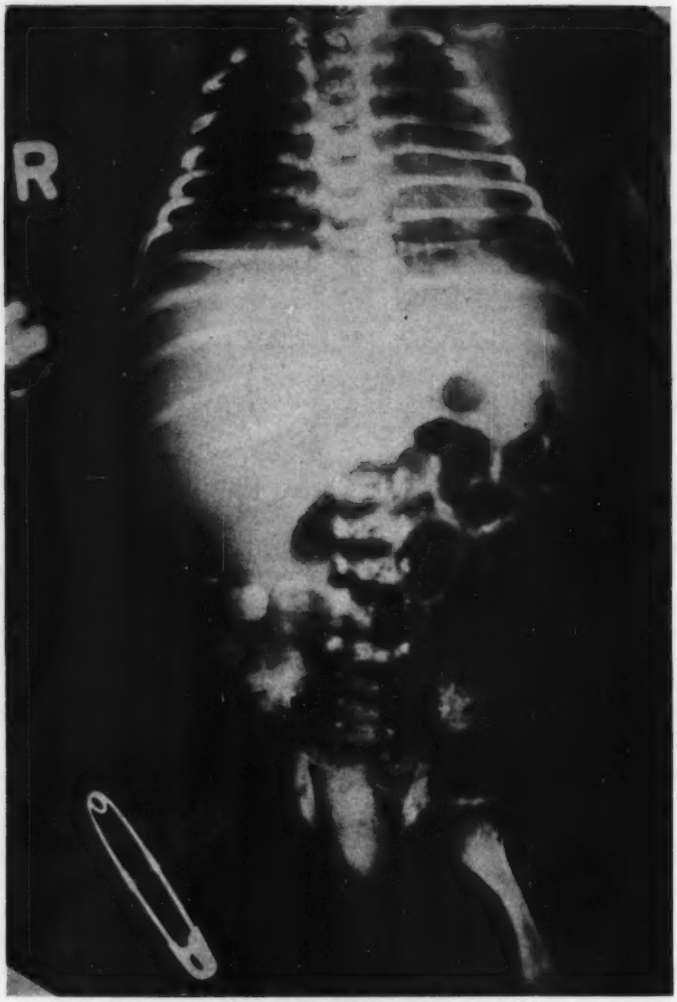

FIG. 2: C. G. Thirty minutes after the intravenous injection of dye reveals the dilated calices with inferior displacement of the right kidney by a large space-occupying mass in the right quadrant.

large, moderately firm mass in the right upper quadrant and part of the right lower quadrant. A definite relationship of this mass to the liver was not determined. Otherwise the physical examination was negative.

Laboratory data revealed a hemoglobin of 11 grams; the white cell count was 19,300 with 24 per cent neutrophiles. Urinalysis on two occasions showed many white blood cells. A flat plate of the abdomen revealed a large shadow involving the entire right side of the abdomen. Pyelographic examination showed the intestines to be displaced to the left. The calices and pelvis on the left were not clearly visualized; however, on the right side the calices were markedly enlarged and the kidney was displaced downward into the pelvis. A chest x-ray was negative.

An exploratory laparotomy was performed on January 7, 1949. A large retroperitoneal mass, the size of a small grapefruit, was seen just below the liver. The tumor mass, weighing 145 grams, was removed.

The tumor was oval, well encapsulated, and measured 8.1 x 7.2 x 5.0 centimeters. At one pole was a hemorrhagic portion measuring 2 x 3 centimeters, which appeared to be kidney. On hemisection, blood escaped from the small area described and a rim of kidney tissue about 6 centimeters wide was seen. The remainder of the mass was composed of yellowish white myomatous tissue interspaced with small hemorrhages. On microscopic examination, the tissue was made up of nearly uniform type of oval or elongated cells with a rather vascular nucleus, occasionally in mitosis. In one section a rim of kidney tissue with some evidence of a capsule separating the tumor and renal tissue was observed. The neoplastic tissue was embryonic in type and apparently of mesoblastic origin.

The hospital course was uneventful. The infant was maintained on subcutaneous fluids for 18 hours after operation and then oral feedings were started.

He was discharged on January 10, 1949, the seventh hospital day. Deep x-ray therapy was started on the following day; the infant received twenty treatments of 140 units each to the anterior and posterior right abdominal part. The factors were 200 Kv, ½ millimeters of copper and 4 millimeters of aluminum through an 8 x 8 portal. At first, treatments were given daily, but due to nausea and vomiting experienced by the baby, it was found necessary to give treatments every other day.

Since discharge the child has remained well with the exception of a physiological anemia of prematurity which has been treated with iron and two small transfusions. No evidence of metastases has been found to date.

COMMENT

The chance finding of an abdominal mass by the mother is often the first symptom in cases of Wilms' tumors. In this case investigation of apparently minor symptoms revealed a rapidly enlarging mass which was removed surgically within ten days after first recognition. This

reaffirms the necessity of careful palpation of the abdomen in all routine examinations.

Throughout hospitalization the infant was handled as an emergency case with restriction of examination and palpation of the abdomen to a minimum. It is to be hoped that this method of handling, plus the early recognition of the tumor will contribute to a final favorable outcome.

SUMMARY

A case of Wilms' tumor in a five weeks old premature infant is presented. The importance of early recognition, and the emergency method of handling such cases is emphasized.

REFERENCES

1. Kretschmer, Herman L.: Surgery of the Genito-Urinary Tract. Brennemann's Practice of Pediatrics. W. F. Prior Co. 1947.
2. Ewing, J.: Neoplastic Diseases, W. B. Saunders Co. 1928.
3. Burdick, W. F., et al: Symposium on Wilms' Tumors. Medical Annals of the District of Columbia, **17:** 559, October 1948.

NON-THROMBOCYTOPENIC PURPURA

Case Report No. 154

Harold W. Bischoff, M.D. J. A. L. 48–11798

This 6 year old colored female entered Children's Hospital on October 14,1948 with a chief complaint of swelling of the feet and legs, pain in the left side and limping on walking of 4 days duration.

The patient was well up until October 10, 1948, four days prior to hospital admission, when upon coming in from play, it was noticed that she was limping and the left leg was swollen over its lateral aspect. The following day the girl went to school. By evening both feet were said to have been swollen and there was pain from the ankles to the knees. The local application of chloroform liniment prescribed by a private physician gave no relief.

On October 12, 1948, the child was seen in the Children's Hospital Dispensary where the recommendation was made that the child return for further study or hospitalization.

There was no history of recent fever or upper respiratory infection. On the second day of the present illness the child vomited once. The character of the vomitus was not noted. The evening before hospital entry the child complained of headache. The family, birth and developmental histories were non-contributory.

This had been the child's first illness. No history of allergy was obtained. In the dietary history it was found that the child was first given orange juice when she began to walk at approximately one year of age. There had been adequate intake of citrus fruits and the child had had an increased intake of orange juice during her present illness.

In the social history it was noted that an outside toilet was used and that there were rats in the house.

Physical examination revealed a well developed, well nourished colored female of stated age lying quietly in bed in no apparent distress. The child was cooperative, well oriented, answered questions readily, and volunteered information about her symptoms. The skin was warm, of smooth texture and contained some small areas of depigmentation on the lower anterior chest. There was generalized lymphadenopathy, including the left epitrochlear gland. The pupils were round, regular and equal and responded to light and accomodation. The extraocular movements were normal. The fundi showed a normal size in relation between the arteries and veins and no hemorrhages or exudates were present. The heart was normal and the blood pressure 86 systolic over 66 diastolic.

The back was very tender on the left side over the lumbar region extending up to the left costo-vertebral angle. There was a definite swelling in the left side which was approximately as wide as the erector spinal group of muscles. Pressure over this area caused the child to complain bitterly and her pulse rate to increase. When the child was struck lightly on the top of her head with a clenched fist, pain was experienced by the patient over the area of swelling; however, there was no radicular radiation of the pain.

The abdomen was flat and the liver, spleen and kidneys could not be palpated. As the examining hand was carried laterally to the left flank some muscle spasm was encountered and the child complained of pain. The skin over both knees was warmer than that over the remainder of the legs and thighs. The skin over the inner aspect of the right ankle was somewhat warmer than the remainder of the foot. The child complained of pain in both knees which appeared to be swollen. However, both knees could be moved passively through all their ranges of motion without pain. Straight leg-raising could be done with either leg, and without resistance applied causing no increased pain in the back. Positional sense and epicritic sensibility were normal.

At the time of entry, a hemogram disclosed 11 gms. hemoglobin with 3.9 million red blood cells, 7,850 white blood cells and with the exception of 4% eosinophils, a normal differential. The 3 plus acetone in the urine revealed on entry was the only finding of note in the urinalysis. The blood Kahn and Mazzini were negative. A blood sedimentation rate at entry was 20 mm. per hour.

The evening of her hospital entry, the child was seen in cardiac consultation. The cardiologist suggested that a therapeutic trial be made of aspirin, 20 grains, that night and 20 grains the following morning. By morning the back pain was absent. The swelling over the left lumbar region had subsided and the child no longer had pain in any joint. That same morning a flat film of the abdomen and films of the knees and ankles revealed no abnormalities.

On the second hospital day the child first complained of aching pains in the abdomen. The pain continued for about 36 hours and was distributed over both lower quadrants of the abdomen. A blood count and sickling preparation taken the evening of the day of onset of abdominal pain showed a normal blood count with 1% eosinophils and no sickling of the red blood cells.

On the third hospital day the child vomited about 75 cc. of dark brownish-yellow fluid with some small red clots which appeared to be blood. Two hours later 125 cc. of the same type material was vomited. The specimens were sent to the laboratory which reported the benzedine test to be

strongly positive for blood. Later in the afternoon the child passed one watery stool which contained some mucus and what looked and smelled like blood. A rectal swab culture was taken which was subsequently reported as negative.

On the evening of the third hospital day the child was seen by a member of the surgical house staff who did not feel that the abdominal symptoms were representative of an acute surgical abdomen.

The evening of the fourth hospital day the child developed a papular petechial-like rash over the buttocks, elbows, dorsum of the feet and the lateral aspects of the legs. The rash developed as it was being observed and in some areas the papules diminished in height, became macular and in some areas coalesced. It should be said at this time that the temperature had never been elevated nor was it elevated at the time of the appearance of the rash. A blood count taken a few hours after the appearance

TABLE I

Bleeding time	1 minute
Venous clotting time	7 minutes
Clot retraction time	2 hours
Blood vitamin C level	1 mgm. %
Prothrombin time	100% of normalcy
Platelets	400,000 per cu. mm.
Red blood cell fragility	Hemolysis began 0.48% NaCl Hemolysis ended 0.32% NaCl
Control	Hemolysis began 0.50% NaCl Hemolysis ended 0.36% NaCl

of the rash showed 12,000 white blood cells (8% eosinophils) and 150,000 platelets per cu. mm.

The following day the Rumpel-Leede test was found to be positive; approximately 10 petechiae developed during the five minutes that the tourniquet was applied.

In order to have a more complete evaluation of the blood picture, additional laboratory tests were performed. These are summarized in Table I.

A repeat red blood cell sedimentation rate showing a rate of 22 mm. per hour confirmed a previous sedimentation rate of 21 mm. per hour.

The temperature rose to 101°F on the 6th and 7th hospital days. On both of these days the child was very well. On the 7th hospital day an electrocardiogram was taken and this was reported as normal. A chest film and x-rays of the long bones taken on the 7th hospital day were interpreted as being within normal limits.

On the 11th hospital day, benadryl 25 mgm. three times daily was started.

After six days on benadryl medication the rash gradually faded, first on the elbows, then over the buttocks and lastly over the legs and dorsae of the feet, i.e. in reverse order of the manner in which it appeared.

During her hospitalization the child received a total of 60 grains of aspirin. Of this, 40 grains were given during the first 19 hours and the remaining 20 grains in 5 grain doses during the ensuing 3 days.

The child was discharged on the 21st hospital day; the purpuric rash had faded entirely.

DISCUSSION

William S. Anderson, M. D.: Purpura may be defined as a tendency to spontaneous hemorrhage which may be cutaneous, subcutaneous, internal, or involve the mucous membranes. The older classifications grouped symptomatic cases in conjunction with some other pathological process or designated the site of bleeding.

The newer classification, which is much simplified, is based on the pathogenesis or etiology of the bleeding as in the following brief outline:

I. Thrombopenic purpura with diminution of the blood platelets. This may be due to various reasons such as "toxic suppression" of the bone marrow; toxic agents, such as arsphenamine, benzol, radium and x-ray; diseases of the blood-forming organs and idiopathic thrombopenic purpura.

II. Purpura due to capillary damage or weakness. Infections—bacterial endocarditis; eruptive fevers—measles, scarlet fever, vaccinia, typhus, chicken-pox or epidemic meningitis; poisons—phosphorous, quinine, potassium chlorate; mechanical—convulsions, pertussis, after bandages or splints; scurvy; cachectic purpura due to malnutrition and dehydration, and neurological conditions (rarely).

III. Anaphylactoid or non-thrombocytopenic purpura, which seems to fit the case reported today for the following reasons: Variable skin lesions which were described as petechial, purpuric, erythematous, urticarial, and maculo-papular; abdominal pain which was associated with some hematemesis and later melena; arthritic symptoms which were early and fleeting; no reduction in the platelets, and differential diagnosis with many symptoms which were very suggestive of rheumatic fever.

This patient described in the case report seems to fit into the classification of anaphylactoid purpura, although rheumatic fever cannot be completely excluded at the present time. There was no history of any previous allergic manifestation and no preceding illness or dietary indiscretion. There was no history of any drug intake which might have precipitated the present difficulty. The eosinophilia was equivocal and the response to antihistaminics was not striking.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: D. Joseph Judge, M.D.
Edwin Vaden, M.D.
By Invitation: Robert Sullivan, M.D.

Dr. Judge: L. D. 45-6373

This 26 month old colored male child was admitted to the hospital with the chief complaints of foul smelling stools and abdominal swelling of about one month duration.

Approximately a month before admission it became apparent to the child's mother that there was an increase in the size of his abdomen. The abdomen had always been a little large in comparison to the remainder of the skeleton. At that time the child had a mouth infection and a slight fever and when this had cleared, (on an unknown medication), the abdomen seemed to decrease in size. After a week of good health the child had intermittent enlargement of the abdomen and what appeared to be moderate wasting of the extremities. The stools, which previously had been normal, became large, light in color and very foul smelling. There was one short episode of diarrhea but this was attributed to the use of laxatives.

The patient was born at home in a southern state having access to modern medical facilities. The birth weight and early feeding history is unknown and details of development prior to the onset of the present illness were not clear. Dietary history revealed inadequacy of protein foods and probably minerals and vitamins.

The family history showed that when the child was twenty months of age his mother died of tuberculosis. There was no other family history.

Physical examination on admission revealed the temperature to be 99° F., pulse 110 and respirations 23. The weight was 10 kilograms and the height 88 cm. The child appeared cachectic and emaciated with loosely fitting skin, a loss of subcutaneous tissue and muscle, wasting of the buttocks and legs with the latter spindle-like. The abdomen was enlarged, moderately hard and tense. Beading of the costochondral junctions and flaring of the lower ribs was noted. The tongue was smooth and the tonsils enlarged slightly. There were small shotty posterior cervical, axillary and inguinal lymph nodes. No abnormalities of the heart and lungs were noted. Rectal examination was negative.

Laboratory work was as follows:

Hemoglobin	7.5-9 gms.
Erythrocytes	3.2 million (average)

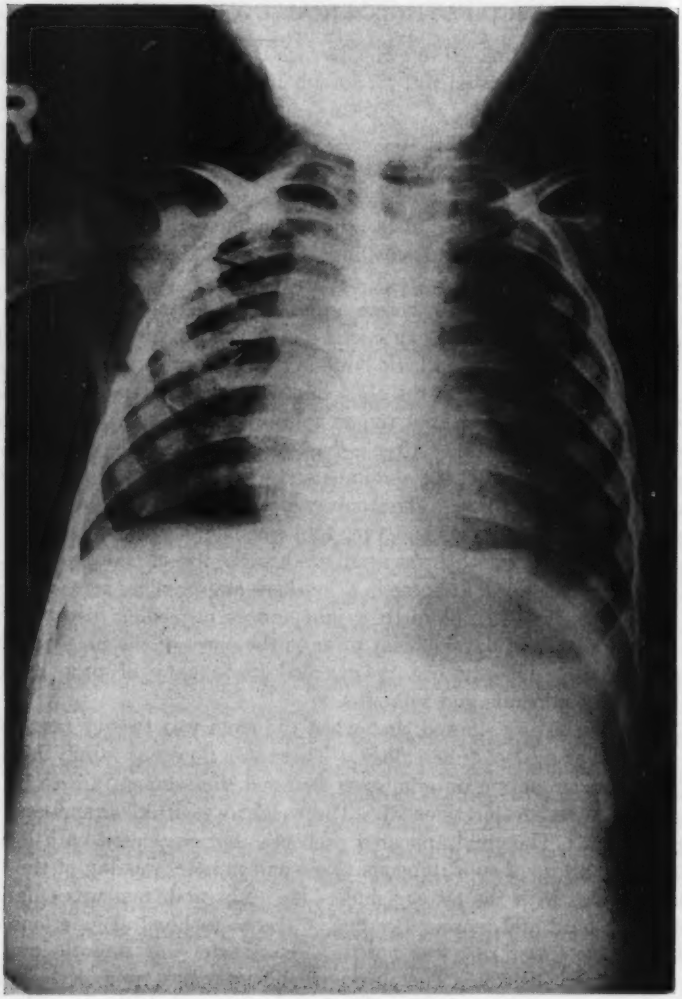

FIG. 1: L. D. Please refer to conference report

FIG. 2: L. D. Gastrointestinal study 1½ hours after the ingestion of barium showing the marked disturbance in mucosal pattern of the jejunum and ileum. Disturbances of the normal lumena of the lower small bowel are reflected in clumping and marked irregularities with considerable shift of the small gut to the left. There is some thickening of the abdominal wall.

Leucocytes	10,600 average
Differential	54% neutrophiles
Sedimentation rate	37 mm/hr (Wintrobe)
Urinalysis	Negative
Stools	Normal fats and starches
Mantoux test (second strength)	Positive
Prothrombin	50% normal
Ceph. Flocul	Negative
Serum calcium	8 mgm. %
Phosphorus	4 mgm. %
Acid phosphatase	3–King-Armstrong units
Cholesterol	165 mgm. %
Gastric washings	Negative for acid fast bacilli

X-ray examination of the chest on admission showed a small area of infiltration in the second right anterior interspace. The bilateral supracardiac shadow was irregular. Flat plate of the abdomen showed a gaseous distention of the entire bowel. Barium enemata revealed displacement upwards of the entire transverse colon. X-ray of the long bones was negative.

The child ran a low grade temperature (99–101°F.) during the first two weeks of hospitalization, with the appetite and general condition fair. At that time rectal examination disclosed the definite presence of a fairly well fixed, firm right lower quadrant mass, an observation which had been made by another physician at the time of the patient's admission, but thought then to be insignificant.

The treatment had been confined to transfusions, penicillin and sulfadiazine but no change was noted in the clinical course. A flat plate of the abdomen at that time was reported as negative. A gastro-intestinal x-ray examination with barium revealed the stomach and duodenum to be normal with the mucosal pattern of the former to be rough, broad and coarse. There was 40 per cent retention of barium at the end of 1½ and 2 hours. The intestines were displaced to the left instead of towards the center of the abdomen.

Repetition of the hemogram showed an anemia. The urine was negative. The stools continued to be large, greenish to brown, usually soft and foul smelling, but examination for fats, starches, ova and parasites was negative. Two glucose tolerance curves were as follows:

FASTING	½ HR.	1 HR.	2 HR.	3 HR.	URINE SUGAR
				mgm. %	
71	77	71	59	65	0
134	174	200	154	112	0

On the 24th hospital day an exploratory laparotomy was suggested.

DISCUSSION

Robert B. Sullivan, M.D.: The chief complaint is always of interest when the diagnosis is difficult. In this case our attention is directed to the abdomen and perhaps specifically to the intestines. We must explain the abdominal swelling and the foul stools which, though described as light-colored in the history, were seen to be deeply colored on inspection. The mouth infection, smooth tongue, beaded costochrondral junctions, gastro-intestinal x-ray studies, and the dietary history all suggest avitaminosis. The heavy exposure to a dying mother and the positive tuberculin test make some degree of tuberculous infection definite. This boy had a "brownie build" typical of the coeliac syndrome. His height was 35 inches when we might expect it to be 33 to 35 inches and his weight was 22 pounds when we might expect it to be 27 to 29 pounds. This build and this developmental deficiency is found in the early phase of coeliac disease, in tuberculous peritonitis, in nutritional deficiency and in individuals with abdominal malignant neoplasms. The small, shotty lymph nodes felt in the posterior cervical, axillary, and inguinal regions were probably similar to those felt in the majority of children since they apparently did not have the rounded, "fresh" feel of a significant lymphadenopathy. There was a significant anemia with the red blood count being 2 million on one occasion. The description of the red blood cells and the proportion of band forms and eosinophiles would be of interest. An elevated sedimentation rate is characteristic of tuberculosis but it is also found in most severe infections in children and in the presence of degenerating malignant neoplasms, and in prothrombin deficiencies. It is rarely of much diagnostic help. The prothrombin time is 50 per cent which is moderately abnormal and suggests either liver dysfunction, dietary inadequacy, or poor intestinal absorption. The cephalin flocculation test is a reliable qualitative test for the presence of active liver pathology. This was negative.

The serum calcium is low and the serum phosphorus is normal. This is characteristic of rickets though usually both are low. A low serum calcium is also found in coeliac disease, cachectic states, hypoproteinemia and some other conditions not suggested by this patient's findings. The acid phosphatase is normal. The only information I can draw from this is that carcinoma of the prostate with metastases to the bones is not present. The alkaline phosphatase would be more valuable since a value above 20 units in a child is good evidence of active rickets when the other causes of elevations are excluded. We would like to have the result of a stool culture though this picture is not likely to be presented by an enteral infection with E. typhosus or the paratyphoid, shigella, or salmonella groups. The glucose tolerance tests results are curious. If in the first

test the glucose was given by mouth and in the second it was given intravenously, there is evidence of poor absorption of glucose from the intestines. This could be due to hypomobility of the intestines or to a functional abnormality of the absorption membranes. Coeliac disease would be suggested. In the second test the high fasting blood sugar and the one hour result of 200 mgm. with a negative urine test for sugar are also odd. We must discard the results of both these tests since we don't know under what conditions they were carried out.

The x-ray examinations show evidence of pulmonary infiltration and probably mediastinal lymphadenopathy. Gastro-intestinal mobility is reduced and there is evidence of a large mass in the right lower quadrant. This mass had been definitely felt through the rectum and the diagnosis in this case must explain the mass. Any right lower quadrant mass suggests an appendiceal abscess even in children less than three years old. The absence of an episode suggesting acute appendicitis does not rule this out conclusively. The most common abdominal tumor in this hospital is the Wilms' tumor. Almost invariably palpation of a mass through the abdominal wall precedes other signs of trouble in this condition. Neuroblastoma usually metastasizes early to the bones and liver. Malignant lymphoma cannot be ruled out here but it is not the most likely diagnosis. In older patients actinomycosis may be responsible for a mass in this region. Histoplasmosis causes granulomatous masses in the intestinal mucosa.

If we discard the glucose tolerance tests, all of the abnormal findings can be explained by two diagnoses, tuberculosis and avitaminosis.

Diagnosis:

1. Tuberculosis
   - Pulmonary
   - Mediastinal adenitis
   - Mesenteric adenitis
   - Peritonitis with a plastic exudate mass in the right lower quadrant
2. Avitaminosis

Other possibilities are appendiceal abscess and retroperitoneal malignant lymphoma. I believe this child did not have coeliac disease.

PATHOLOGICAL DISCUSSION

John E. Cassidy, M.D.: Dr. Sullivan has covered the possibilities thoroughly and has given a complete and interesting discussion. We should begin our part of the story by saying that this patient had been considered to have coeliac disease until a short time before death. The possibility of a tuberculous process was relegated to the background despite a definite history of contact, a positive tuberculin test and the demonstra-

tion of a suggestive pulmonary lesion. Dr. Sullivan has mentioned the significance of a positive tuberculin test in this age group and we would like to re-emphasize its importance. A positive tuberculin test in a two year old child means that there must be living tubercle bacilli present—and most likely an active tuberculous process.

Unfortunately an autopsy was not performed. But the pertinent information was obtained when the laparotomy was performed. The peritoneal cavity was opened and the intestines were found matted together by a plastic exudate. There was a large mass in the right lower quadrant with many fibrous adhesions about it. A rounded nodule, about four millimeters in diameter was removed. It was grayish pink in color and firm in consistency. Microscopic examination of this tissue revealed typical tubercles with marked caseation and numerous Langhans-Schüffel giant cells.

We are certain that this patient had tuberculous peritonitis with a mass in the right lower quadrant, and most likely pulmonary tuberculosis with mediastinal lymphadenitis.

We can all learn a lesson from this case if we will. As Dr. Sullivan has so clearly brought out in his discussion it is well to pay attention to the more common diseases in attempting to make a diagnosis. All too frequently we are too anxious to make an unusual diagnosis and in so doing overlook the real trouble.